PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The effect of plant milk consumption on childhood growth: protocol for a systematic review
AUTHORS	Soczynska, Izabela; da Costa, Bruno; O'Connor, Deborah L; Jenkins, David; Birken, Catherine; Keown-Stoneman, Charles D.G.; D'Hollander, Curtis; Calleja, Sabine; Maguire, Jonathon

VERSION 1 – REVIEW

REVIEWER	Merritt, Russell J University of Southern California
REVIEW RETURNED	17-Feb-2023

GENERAL COMMENTS	This succinct protocol is nicely written and appears to follow guidelines established for the conduct of such studies. Having reviewed at least some of this literature in the recent past, I am not optimistic that the investigators will find extensive information related to their stated objectives. However, even better quantifying the gaps in our knowledge regarding the impact of plant based milks on the growth of children can be of value. The authors plan to use the age of the child as a variable in the assessment of the role of plant based milks in the diet. As noted recently [JPGN 2020;71(2):276], that is very important in the role such milks play in the diet and any potential for adverse effects. There are some potential limitations to the research protocol. Any analysis that pools data on various sources of plant based milks is mixing apples with onions. For example, there really is no similarity in the nutritional composition of a typical soy based milk and almond milk, even when “fortified.” It can also be important to identify the specific plant based milk product used, because there are varying compositions and degrees of fortification of these beverages and the largely unknown factor of how bioavailable fortified nutrients may be. To do any analysis that pools all of these plant based milk sources in examining effects on outcomes will likely be nonproductive. Another variable that hopefully the study design will be able to address is how the plant based milk is used in the diet, per diet diaries and food frequency questionnaires. It is helpful to know the quantity of milk, and the rest of the diet that complements the plant based milk. The situation of a 10 year old omnivore consuming a glass of soy milk daily is not in any way similar to a two year old vegan consuming 3 cups of almond milk daily. Some children are given plant based milks in the context of multiple food allergies, and any indication the plant based milk was used to prevent allergic symptoms would be helpful. The diet and the nutritional role of the plant based milk in the diet of such subjects can be quite different

	from those of a child on an unrestricted diet. Indeed, such patients have been reported to have slower growth. All of these dietary and clinical variables only tangentially related to the plant based milk have potential to influence growth and nutritional status. To the extent they can be considered in the analyses performed, the conclusions will be more informative.

REVIEWER	Perez-Cueto, Armando Umeå Universitet, Food, Nutrition & Culinary Science
REVIEW RETURNED	24-Feb-2023

GENERAL COMMENTS	Authors should also mention that a large proportion of the population has different allergies to milk protein or intolerance to milk components e.g. lactose (PMID: 30558337). Therefore, many families require beverages without milk/dairy for their children. This view has not been taken in the justification of the paper. Many populations also in USA and Canada are naturally intolerant to cow's milk & derivatives. If authors' starting hypothesis is that cow milk is superior, this constitutes a high risk of reflexivity bias. Furthermore, breastfeeding should not be an exclusion criteria, as BF can be carried over together with the plant-milk (overlap period). Both plant-based and breast milks can be complementary to each other (PMID: 27336781; PMID: 33330129). Mother's breast milk is considered vegan (PMID: 32319307). For outcome, it is more important that child has followed her growth line steadily. Hence the anthropometric trajectory of the child should be a better indicator, rather than a point in time. PMID: 31334762; PMID: 25476426 PMID: 30368858 PMID: 36448333 PMID: 35665226 Funding by dairy is of a concern, hence all authors are expected to report on their own reflexivity bias. This needs to be mentioned in the protocol, and further discussed in the paper (PMID: 30849272; PMID: 11513933; PMID: 17606171). Authors need to disclose their point of departure, and their own beliefs regarding the matter of the review. Authors should consider more holistic papers in their justification, and probably more recent ones (PMID: 32095830; . There are recommendations in Europe for practitioners on vegan diets, e.g. Vechi Study in Germany (PMID: 34069944; PMID: 31013738; PMID: 34855006), there are papers by authorities like Willett from Harvard on the benefits or lack-thereof of cow's milk (PMID: 19562851; PMID: 32053300. The argumentation of the authors for conducting this review seems rather narrow. Authors should evaluate recent reviews and meta analyses of diets to bring the big picture (PMID: 36812419; PMID: 30864165).

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comment: This succinct protocol is nicely written and appears to follow guidelines established for the conduct of such studies. Having reviewed at least some of this literature in the recent past, I am not

optimistic that the investigators will find extensive information related to their stated objectives. However, even better quantifying the gaps in our knowledge regarding the impact of plant based milks on the growth of children can be of value.

Response: We appreciate your feedback. This limitation been acknowledged in the 'Strengths and limitations' section as follows: (p. 3 lines 9 to 10) "The study may be limited by few available studies because plant milk consumption in children is a relatively new dietary trend." Nonetheless, as pointed out by the reviewer, a systematic review with limited studies can still offer valuable insights into the current knowledge on a topic. This has been emphasized this in our conclusion as follows:

p. 14, lines 245 to 251
"The certainty of the evidence may be limited by the number and quality of studies. Nonetheless, it is expected that the findings of this review will provide valuable insight into what is known about plant milk consumption in children, help to identify gaps and inconsistencies in the existing literature and areas that require further research. In addition, even with limited studies it may still be possible to draw some conclusions or make recommendations about plant milk intake in childhood which may help parents, dietitians, paediatricians and other healthcare professionals make informed decisions when considering plant milk for children."

Comment: The authors plan to use the age of the child as a variable in the assessment of the role of plant based milks in the diet. As noted recently [JPGN 2020;71(2):276], that is very important in the role such milks play in the diet and any potential for adverse effects.

Response: Thank you for the comment. We agree about the importance of considering the age of the child when evaluating the impact of plant milk consumption on growth. We have cited the mentioned study in our manuscript to support our rationale for conducing subgroup analysis based on the child's age (p. 13, lines 219-220) "If sufficient data are available, we will tabulate the evidence: by the age of children since younger children have a higher risk of nutritional deficiencies [2,3]."

Comment: There are some potential limitations to the research protocol. Any analysis that pools data on various sources of plant based milks is mixing apples with onions. For example, there really is no similarity in the nutritional composition of a typical soy based milk and almond milk, even when "fortified." It can also be important to identify the specific plant based milk product used, because there are varying compositions and degrees of fortification of these beverages and the largely unknown factor of how bioavailable fortified nutrients may be. To do any analysis that pools all of these plant based milk sources in examining effects on outcomes will likely be non-productive.

Response: Thank you for the comment. We agree that pooling data on various types of plant milks is a potential limitation to our study. We have acknowledged this in the 'Strengths and limitations' section (p. 3 lines 12span style="font-family:Calibri; background-color:#ffffff"> to 13): "Pooling data on various types of plant milks that differ in nutritional content may increase the sample size but potentially limits interpretation of findings." To address this limitation, we plan to evaluate the data separately for different types of plant milks. This has been clarified in the 'Additional analysis' section of our manuscript as follows:

p. 13 lines 214 to 218
"If sufficient data are available, we will tabulate the evidence for each type of plant milk since the nutritional content can vary between the different types of products (e.g. soy milk is higher in protein content than almond milk) [4]. A list of different types of plant milks can be found in Table 2."

Comment: Another variable that hopefully the study design will be able to address is how the plant based milk is used in the diet, per diet diaries and food frequency questionnaires. It is helpful to know the quantity of milk, and the rest of the diet that complements the plant based milk. The situation of a 10 year old omnivore consuming a glass of soy milk daily is not in any way similar to a two year old vegan consuming 3 cups of almond milk daily. Some children are given plant based milks in the context of multiple food allergies, and any indication the plant based milk was used to prevent allergic

symptoms would be helpful. The diet and the nutritional role of the plant based milk in the diet of such subjects can be quite different from those of a child on an unrestricted diet. Indeed, such patients have been reported to have slower growth. All of these dietary and clinical variables only tangentially related to the plant based milk have potential to influence growth and nutritional status. To the extent they can be considered in the analyses performed, the conclusions will be more informative.

Response: Thank you for the valuable feedback. We agree that the amount of plant milk consumed, the child's overall diet and the context in which plant milks are consumed (e.g. allergies) are important.

To address this, we have made the following revisions to our manuscript:

- Under the 'inclusion criteria' section we have clarified that only studies reporting the *amount* of plant milk consumed will be considered to help reduce variability in the data and make it easier to compare and synthesize results. The sentence been revised as follows (p. 7, lines 86 to 87): "Studies that report the amount of plant milk consumed (fortified or non-fortified, sweetened or unsweetened) will be included."

- We have updated the 'data extraction' section by adding a column for "confounders adjusted for", which will allow us to determine whether the study adjusted for dietary factors (e.g. total calcium intake) and will take this consideration when assessing the risk of bias. We will now also extract data on the amount of plant milk children consumed as well as the type of plant milk (e.g. soy, almond). The paragraph has been revised as follows: (p. 12 lines 187 to 188): "The following information will be extracted from each study using a standardized data extraction form: the first author, year of publication, country, sample size, age of children**, amount of plant milk consumed (number of cups per day, daily mean intake, etc.), type of plant milk (soy, almond, rice, coconut, etc.), confounders adjusted for** and results (estimates and corresponding 95% confidence intervals for each outcome of interest and p-value)."

- In addition, we plan to explore whether the relationship between plant milk consumption and child growth differs for children with allergies. This has been clarified under the 'Additional analysis' section as follows (p. 13, lines 221 to 222): "If sufficient data are available, we will tabulate the evidence separately for children with food allergies (e.g. to cow milk) which can contribute to suboptimal nutrient intake and poor growth in children [5].

Reviewer: 2

Comment: Authors should also mention that a large proportion of the population has different allergies to milk protein or intolerance to milk components e.g. lactose (PMID: 30558337). Therefore, many families require beverages without milk/dairy for their children. This view has not been taken in the justification of the paper. Many populations also in USA and Canada are naturally intolerant to cow's milk & derivatives.

Response: Thank you for the comment. We have revised our introduction as follows:

p. 5 lines 40 to 43
"Furthermore, some children may be allergic to dairy, lactose intolerant or follow a vegan diet that may prevent them from consuming cow milk [6]. Several studies have emphasized the important role of

fortified plant milks in supporting nutritional requirements (e.g. calcium) of children who do not consume cow milk [5,7,8].”

Comment: Breastfeeding should not be an exclusion criteria, as breastfeeding can be carried over together with the plant-milk (overlap period). Both plant-based and breast milks can be complementary to each other (PMID: 27336781; PMID: 33330129). Mother's breast milk is considered vegan (PMID: 32319307).

Response: Thank you for your comment. We would like to clarify that our study does not intend on excluding children who are breastfeeding. We recognize that there may be a transition period where children consume both breastmilk and plant milks. Our exclusion criteria only pertain to children who consume plant-based infant formulas (commonly referred to as 'breastmilk substitutes') as these differ significantly from plant milk beverages. We apologize for the confusion and have revised the exclusion criteria as follows:

p. 7, lines 89 to 91
“Studies examining plant-based infant and toddler formulas (e.g. soy-based formula) will be excluded as these are specifically formulated to meet the nutritional needs of children and differ from plant milks [9].”

Comment: For outcome, it is more important that child has followed her growth line steadily. Hence the anthropometric trajectory of the child should be a better indicator, rather than a point in time. PMID: 31334762; PMID: 25476426 PMID: 30368858 PMID: 36448333 PMID: 35665226

Response: We agree that growth trajectories provide a more accurate representation of a child’s growth pattern over time. We intend on included any studies that report growth outcomes in children, including those with longitudinal growth data.

Comment: Authors need to disclose their point of departure, and their own beliefs regarding the matter of the review.

Response: Thank you for the comment. We have disclosed the authors competing interests and dietary preferences under the ‘Competing Interest’ section of our manuscript (p. 16).

Comment: Authors should consider more holistic papers in their justification. There are recommendations in Europe for practitioners on vegan diets, e.g. Vechi Study in Germany (PMID: 34069944; PMID: [10]; PMID: 34855006), there are papers by authorities like Willett from Harvard on the benefits or lack-thereof of cow's milk (PMID: 32053300). The argumentation of the authors for conducting this review seems rather narrow.

Response: We have revised our introduction to include a more broad range of viewpoints and perspectives in our justification for conducting this review including the German Vechi Study and a recent viewpoint (published in April 2023) on the potential advantages of plant milk over cow milk. We believe our introduction is much stronger as a result of this feedback and we thank the reviewer for their thoughtful suggestions. The following has been added to the introduction:

p. 4, lines 24 to 27
“Although plant milks are gaining popularity among children, it is not clear whether these beverages offer nutritional benefits for children [11-14]. International guidelines such as those from the American Academy of Pediatrics and Canadian Pediatric Society advise against plant milk consumption in early childhood [15,16].”

p. 5, lines 37 to 45
“Several recently published viewpoints and commentaries have challenged the current guidelines suggesting that children avoid plant milks, claiming that they are misguided and poorly supported, and that plant milks could be beneficial for children (e.g. due to their lower saturated content) [17,18]. Furthermore, some children may be allergic to dairy, lactose intolerant or follow a vegan diet that may prevent them from consuming cow milk [6]. Several studies have emphasized the important role of fortified plant milks in supporting nutritional requirements (e.g. calcium) of children who do not consume cow milk [5,7,8]. Moreover, results of the German Vechi Youth Study have shown that children who follow a vegetarian and vegan diet and consume some or no plant milk still meet their nutritional requirements and attain normal growth [10].”

References

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